

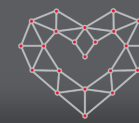
# Research Thrusts and Testbeds

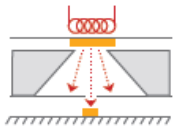
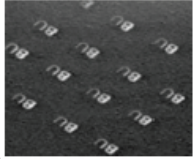
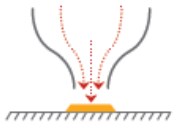
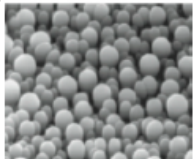
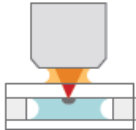
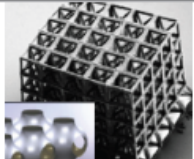
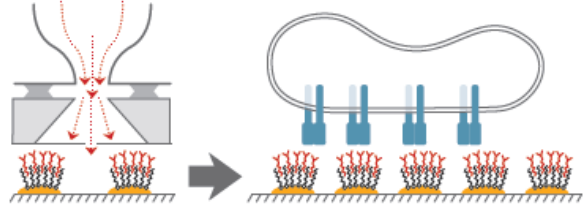

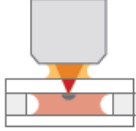
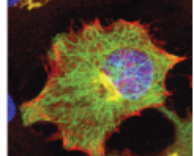
**Christopher Chen**

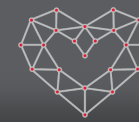
*Director, BU Biological Design Center  
Professor of Biomedical Engineering  
Professor of Materials Science and Engineering  
Harvard Wyss Institute for Biologically Inspired Engineering*



**CELL-MET**

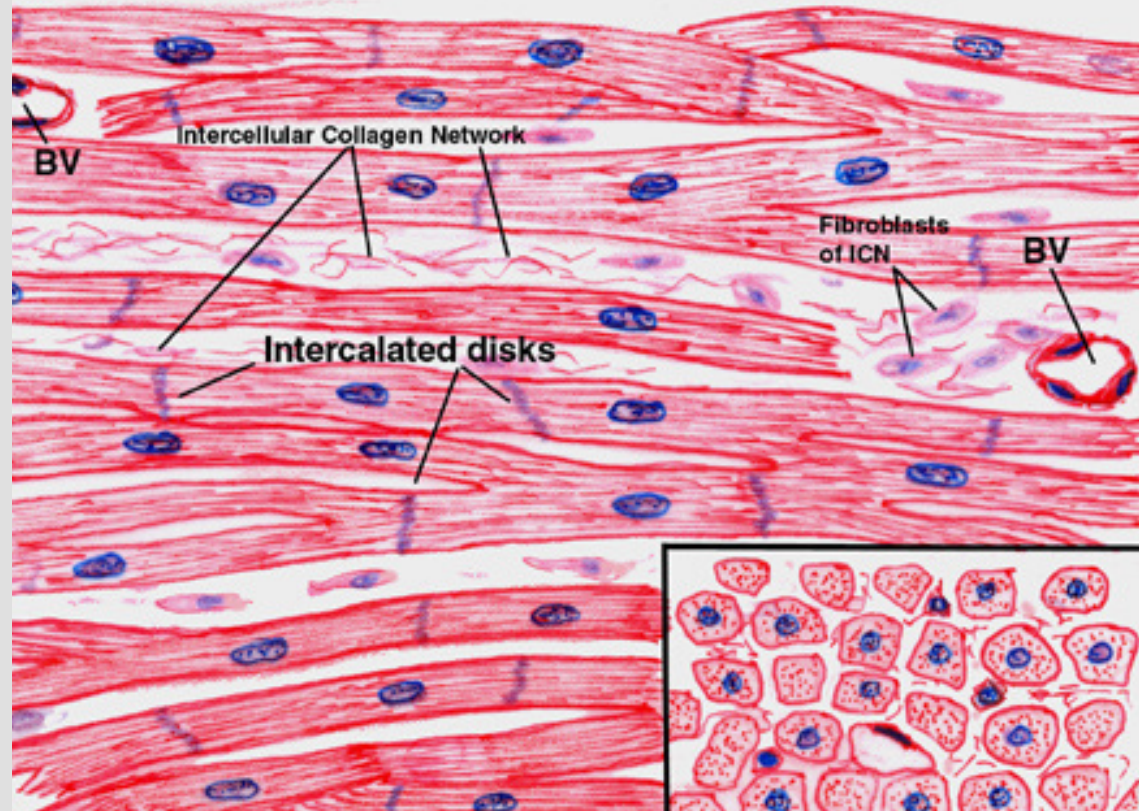


	TECHNIQUE	MATERIALS	STRUCTURES	FEATURE	PURPOSE	WHO
<b>THRUST AREA 1</b>						
<b>Atomic Calligraphy</b>		Au, Ag, Ni, Al, etc.		<50 nm	High resolution patterns of metal that template organic/cellular assembly	BU
<b>OVJP</b>		C60, fluorescent, Pc OTS, HMDS, PEGDA, dPMT, pluronic, thiols, other organics, linear & cyclic RGD		< 2 μm	Functional coatings to create attachment points for cells	UM
<b>THRUST AREA 2</b>						
<b>Nanoscribe</b>		PEG, PEO, PMMA, etc.		<1 μm	3D nanoscale structures to act as scaffolds for cells and sensors/actuators	BU FIU ANL UM
<b>AC + OVJP + Scaffolds</b>				< 50 nm	Patterned 3D structures with focal attachments that direct cell binding, motion and function	BU UM
<b>THRUST AREA 3</b>						
<b>Tissue Assembly</b>				< 50 nm	Complex surfaces and 3D scaffolds for cell binding/proliferation-multiscale, hierarchical, dynamic, embedded sensing	BU Harvard Columbia
<b>THRUST AREA 4</b>						
<b>Imaging &amp; Actuation</b>		fluorescent proteins, quantum dots		< 1 μm	Deep 3D tissue imaging, fluorescent tagging, optogenetic actuation of tissue	BU FIU



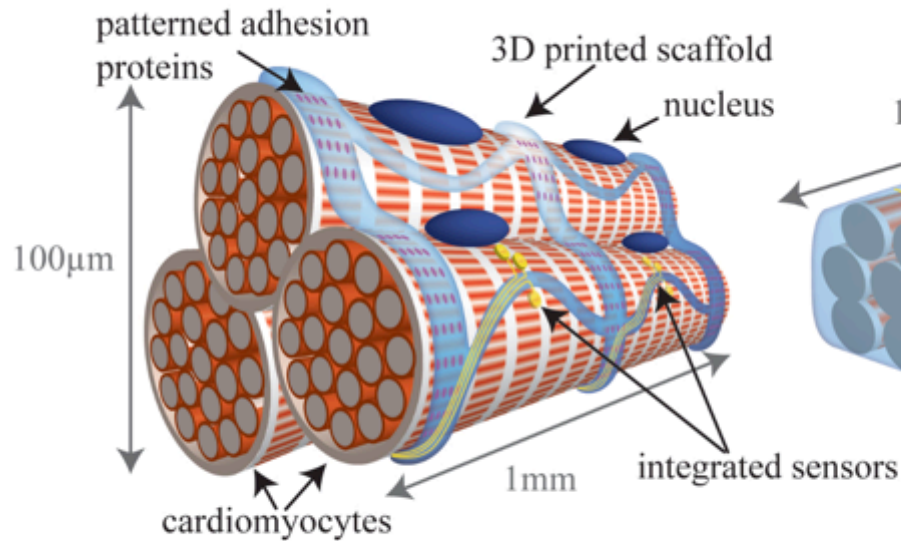
## Functional Syncytium of Heart Muscle

- Mechanically and electrically coupled cardiomyocytes
- Aligned muscle units
- Interwoven microvessels
- Soft extracellular matrix (ECM) scaffolding supports architecture

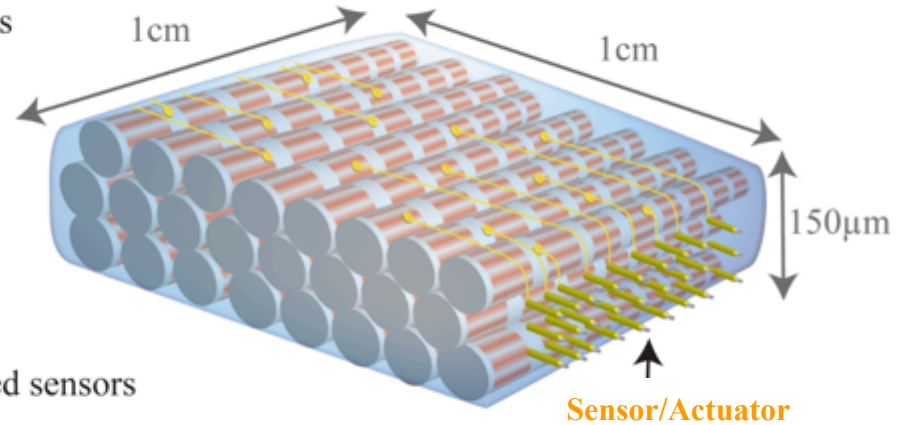




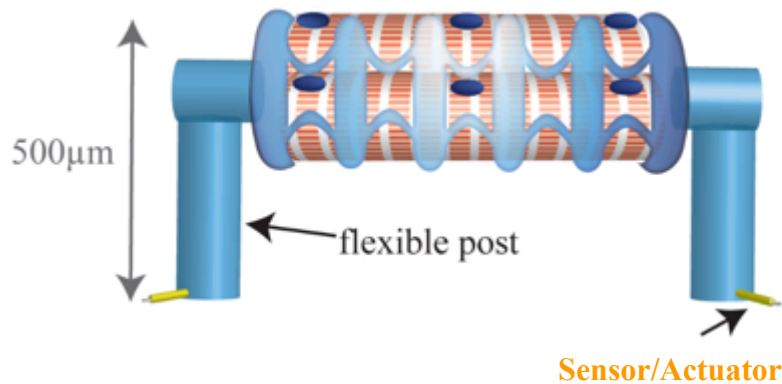
## Cardiomyocytes



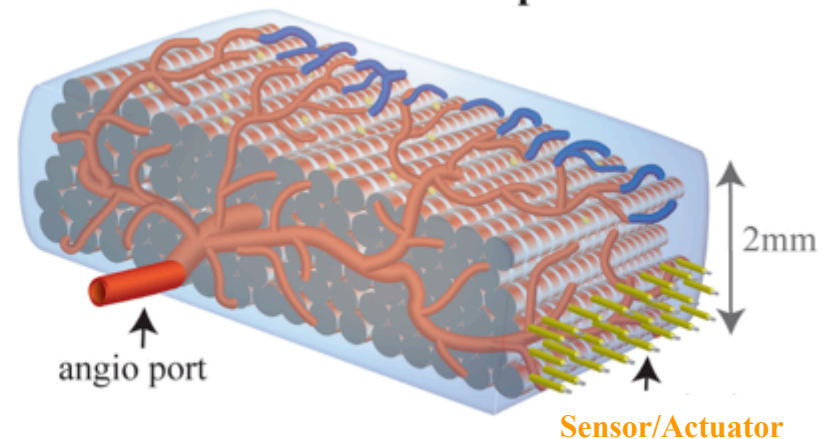
## Instrumented Cardiac Sheet

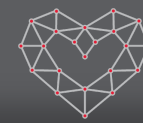


## Cardiac Microbundle



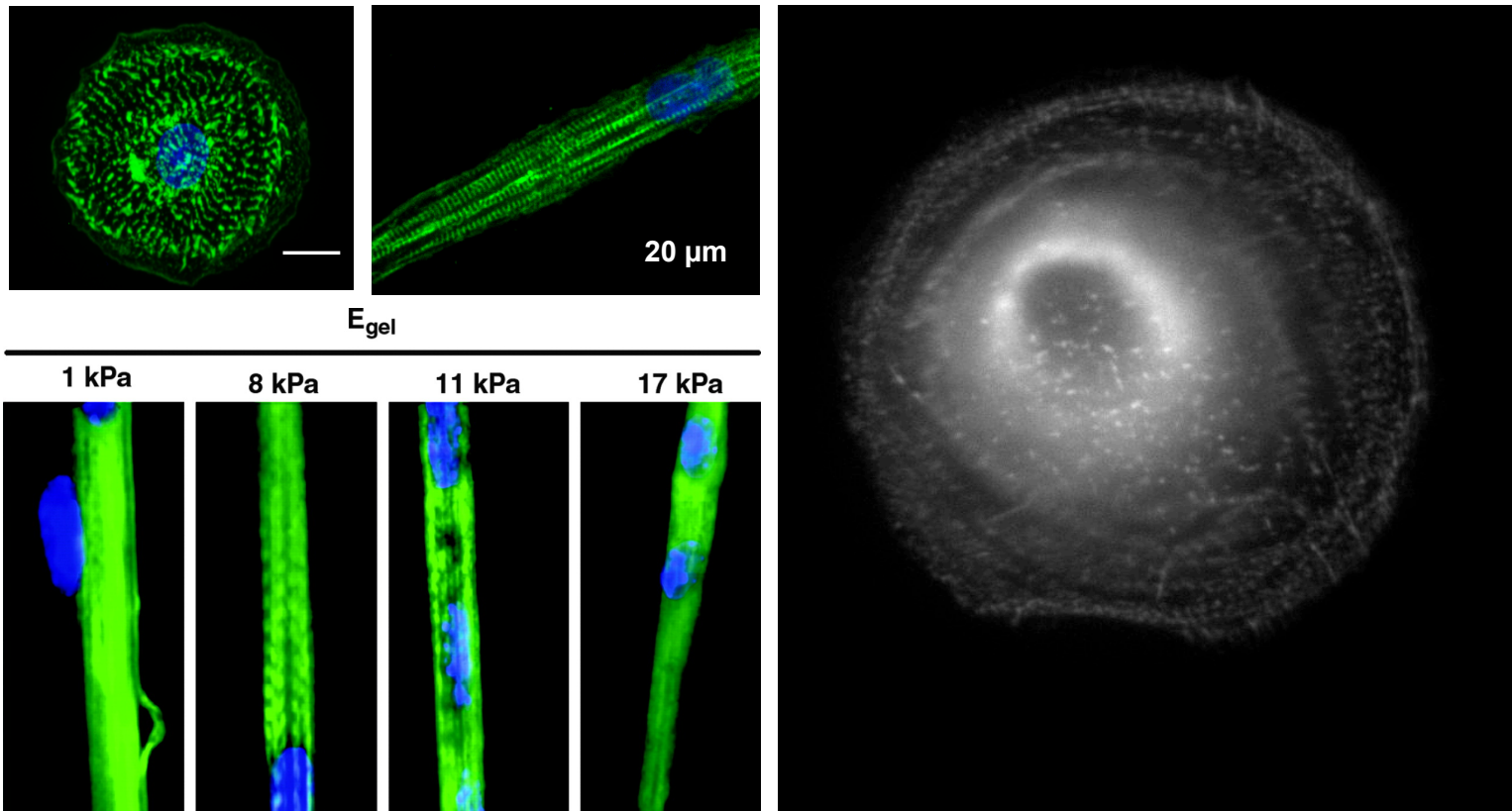
## Vascularized Cardiac Patch

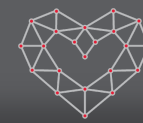




## Pre-ERC: Cardiac cell structure and function are controlled by materials

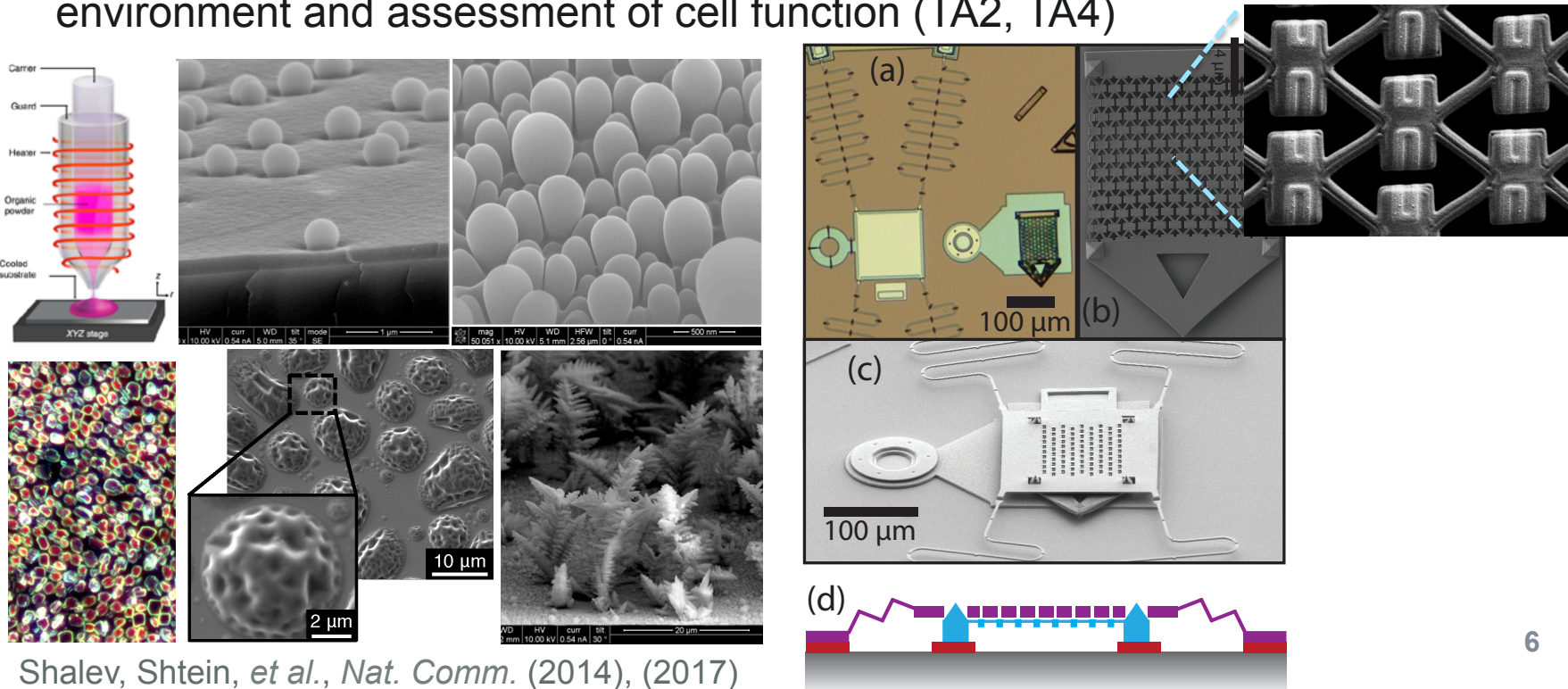
- 1) Patterning cell shape drives cell differentiation, alignment, and mechanics;
- 2) Scaffold stiffness regulates sarcomere maturation and force generation;
- 3) Focal adhesion distribution regulates sarcomere alignment and architecture



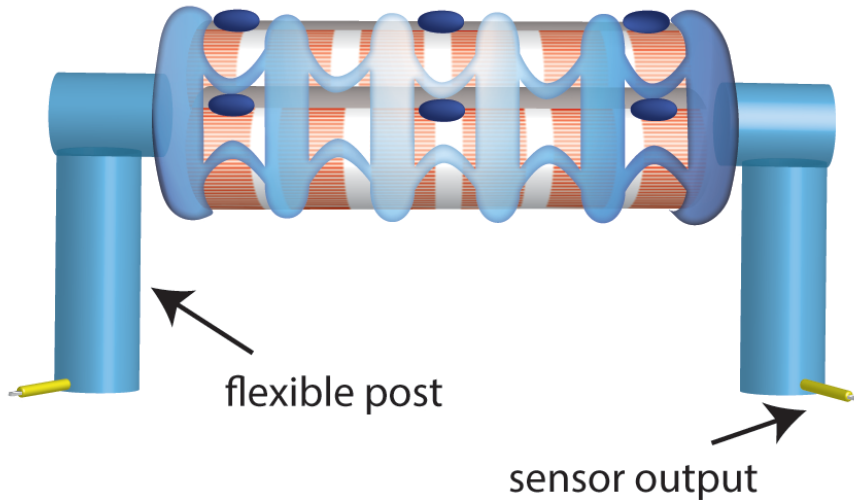
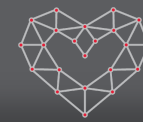


## ERC Goals

- 1) Nanoscale control over cell adhesion will enable control over cell shape, sarcomere architecture, and cardiac function (TA1)
- 2) Controlling scaffold mechanics via both materials and architecture will allow control over cardiomyocyte mechanics (TA2)
- 3) Embedded sensors and actuators will allow real-time modulation of cell environment and assessment of cell function (TA2, TA4)

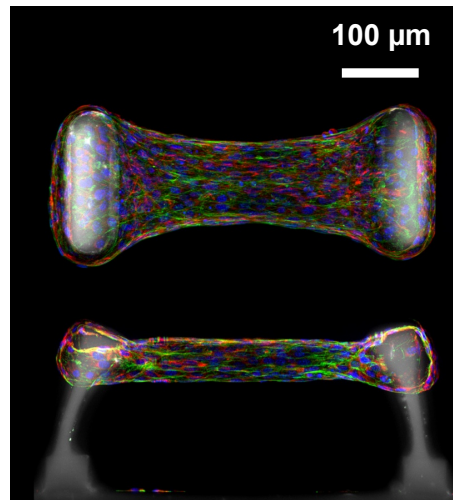
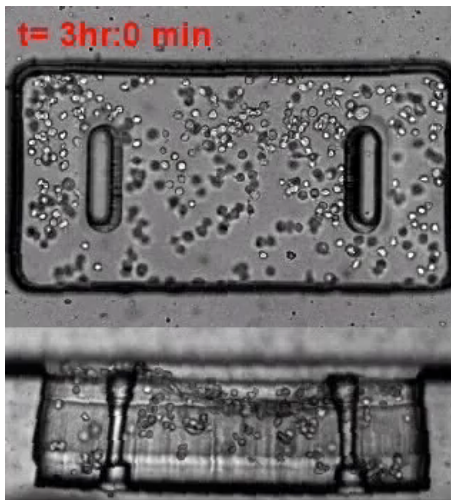


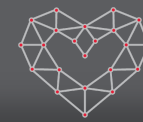
Shalev, Shtein, *et al.*, *Nat. Comm.* (2014), (2017)



## Approach

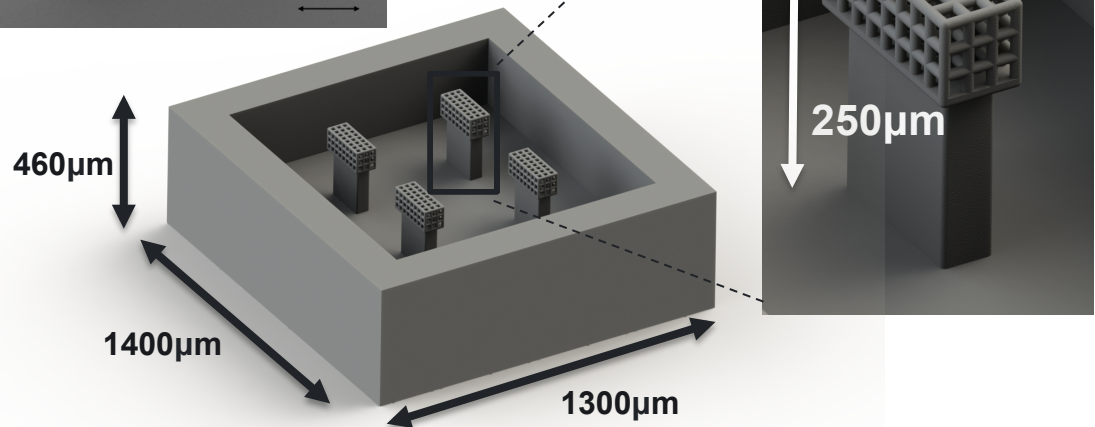
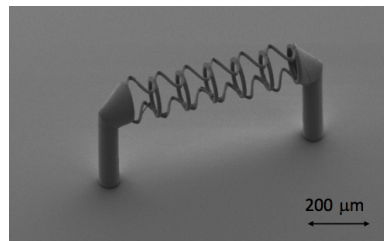
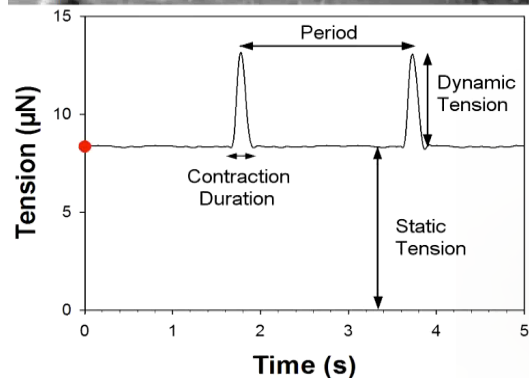
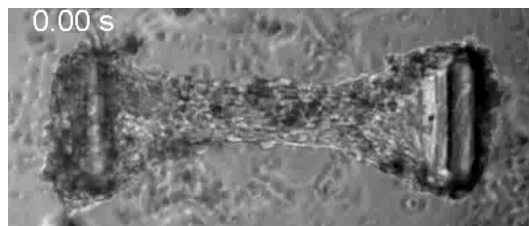
- Control the organization and alignment of cardiomyocytes (TA3), using metamaterials (TA2) and nanoscale adhesive patches (TA1)
- Use actuators (TA1 and TA4) to apply optical and electrical signals, mechanical loads, and structural changes to stimulate the tissue
- Use of feedback loop controls to provide adaptive responses between cells/tissues and their environmental signals
- Iteration based on performance and structural metrics



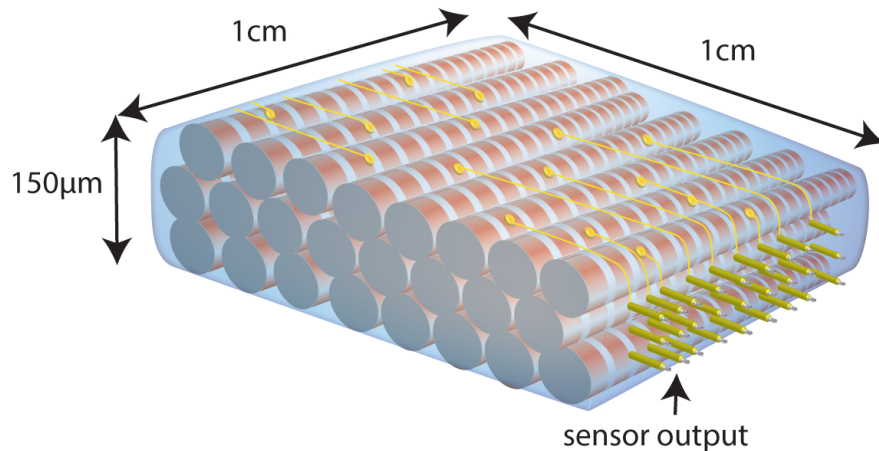
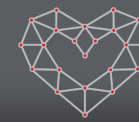


## ERC Goals

- 1) Spatial control over mechanical environment will enable more complex alignments (TA2)
- 2) Specified nanoscale structure and adhesion will enable cell alignment/position control (TA1/2)
- 3) Embedded conduits will enable sensors and actuators (TA2, TA4)

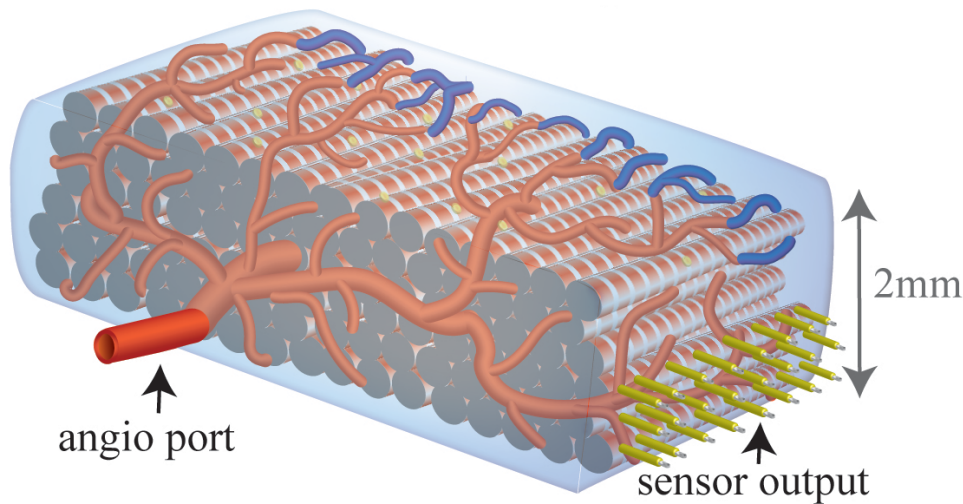
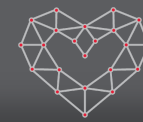






## Approach

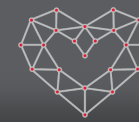
- Control the organization and alignment of cardiomyocytes, as with microbundles, but extended to larger sheets (TA1, TA2, TA3)
- Use actuators to apply electrical signals, mechanical loads, and structural changes to stimulate the tissue (TA1, TA2, TA3, TA4)
- Use embedded sensors and optical approaches to monitor cardiac function, including electrical potential, oxygen levels, pH, material strains, force (TA1, TA2, TA4)
- Use of feedback loop controls to provide adaptive responses between cells/tissues and their environmental signals (TA3, TA4)



## Approach

- Control the organization vasculature and registration with aligned cardiomyocytes; Integration with microfluidic controls to perfuse tissue ex vivo (TA1, TA2, TA3)
- Use embedded sensors and optical approaches to monitor both vascular and cardiac function, including electrical potential, oxygen levels, pH, material strains, force (TA1, TA2, TA4)
- Use of feedback loop controls to provide adaptive responses between cells/tissues and their environmental signals (TA3, TA4)

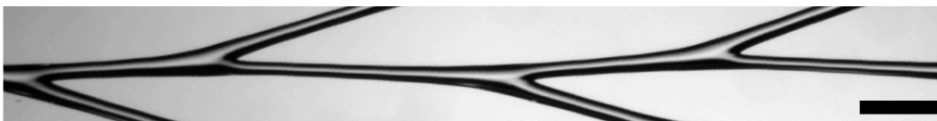
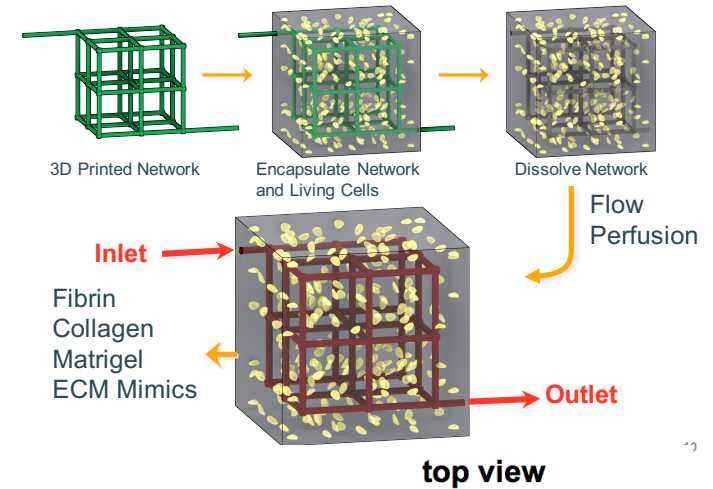
# Vascularized Patch



CELL-MET

## ERC Goals

- 1) Channels branched and tapered down to  $3\ \mu\text{m}$  diameter will match scales of vessels in tissues (TA2, TA3)
- 2) Introduction of embedded sensors and actuators will allow monitoring and manipulation of the engineered tissue (TA1, TA4)

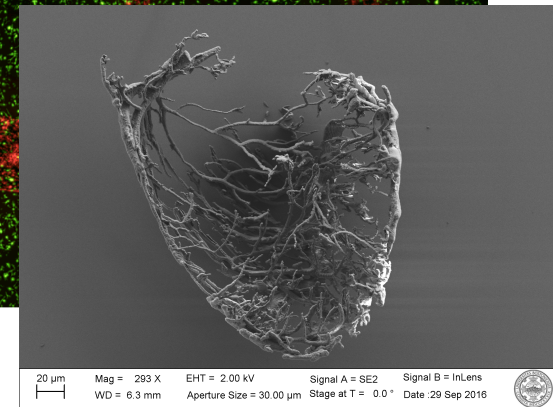
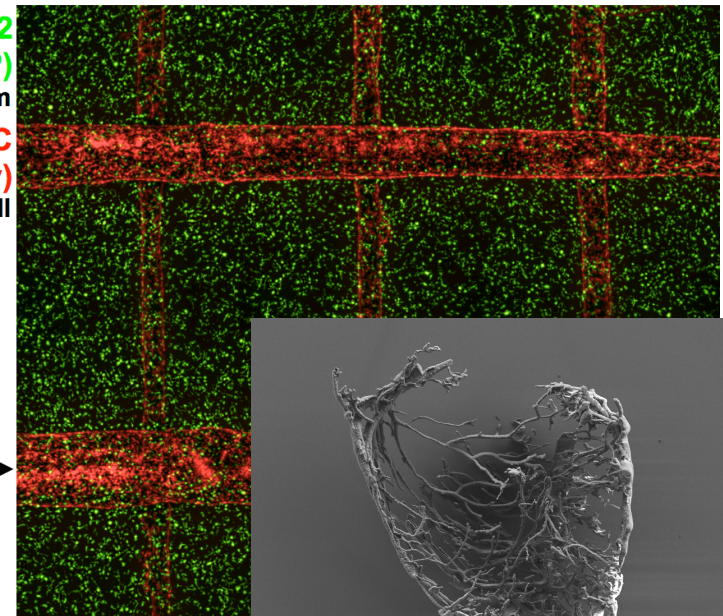


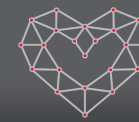
**C**

10T1/2  
(EGFP)  
interstitium

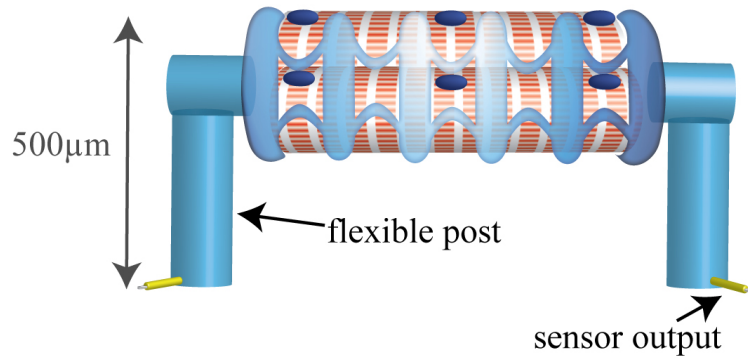
HUVEC  
(mCherry)  
vascular wall

HUVEC  
injection

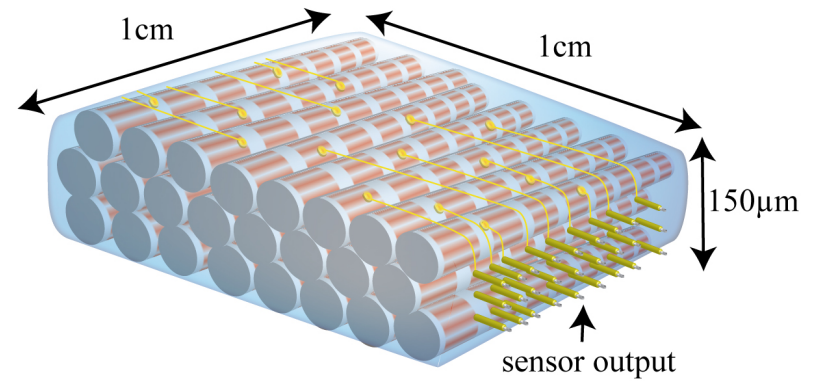




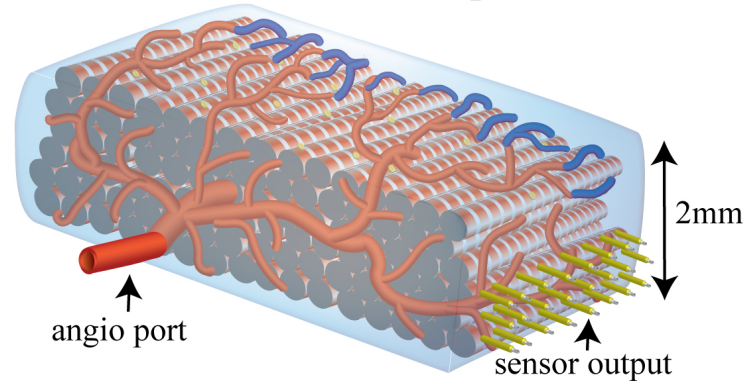
**A. Cardiac microbundle**

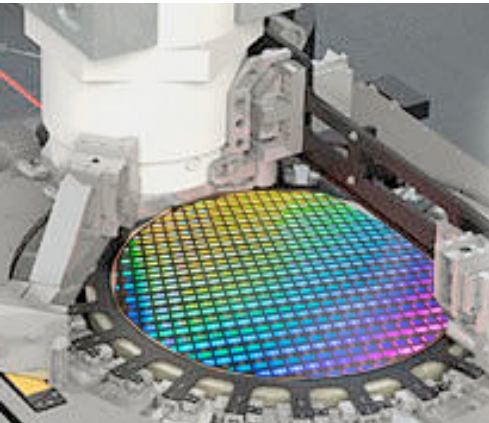


**B. Instrumented cardiac sheet**

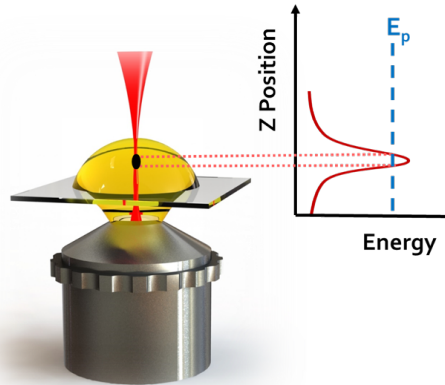


**C. Vascularized cardiac patch**

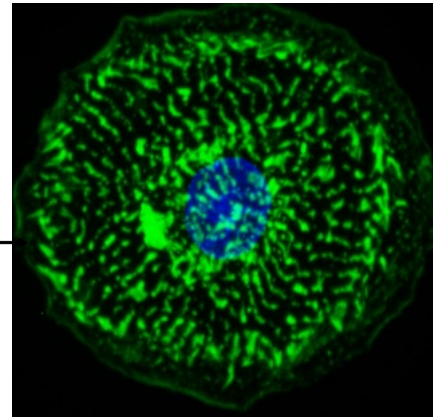




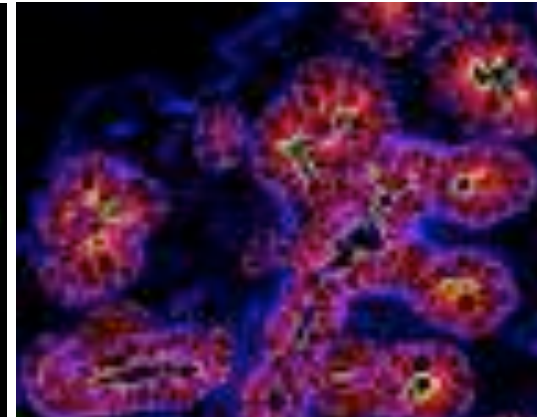
Adhesive  
nanopatterns  
(TA1)



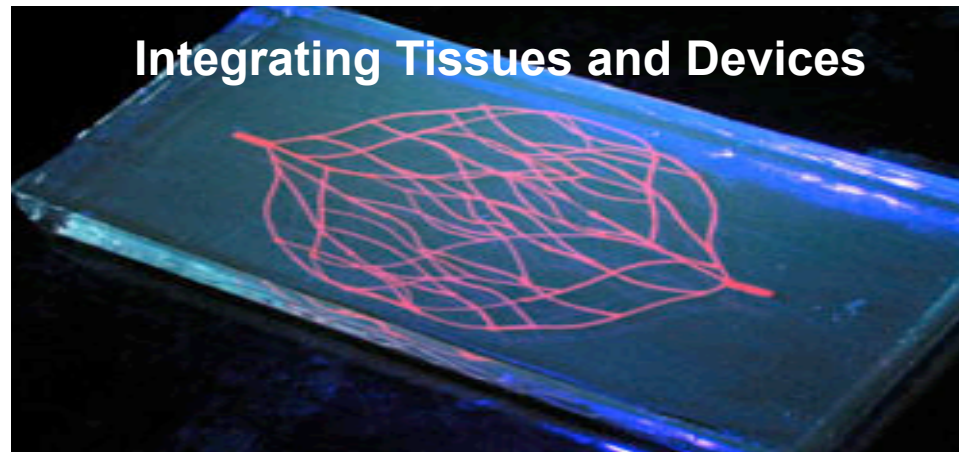
3D  
fabrication  
(TA2)



Cell  
Engineering  
(TA3)

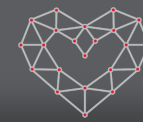


Deep 3D  
(TA4)



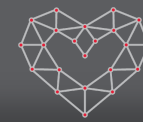
## System level test bed:

- 3D Organs-on-Chip
- Structured Implants



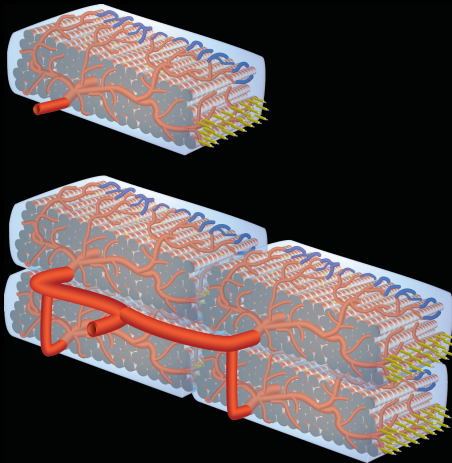
- Understanding the *rules* that govern multicellular organization, how cells → tissues
- Establishing the *technologies* to control tissue assembly
- Engineering human tissues as *models for research* (e.g., *heart-on-chip*)
- Engineering human tissues as *therapeutics for transplant*

→ Provide a foundation for synthetic tissue manufacturing

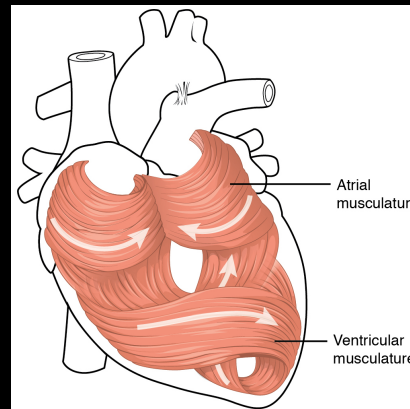


## The Climb Ahead

- **Scale Up**



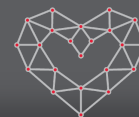
- **Complex muscle architecture**



- **Vasculature**



# Two strategies for heart disease



CELL-MET



## HEART FAILURE:

~5 million Americans

500,000 new cases/year

Annual costs = \$17.8 billion

Prognosis:

75% Die within 8 Years



Sarcomere Proteins  
(TTN, MYH7, MYBPC3, TNNT2, TPM1)

Lamin A/C

RNA-binding motif protein 20

Transcriptional Regulators

Z-disc Proteins

Intermediate Filaments

Dystrophin/Glycoproteins

ATP-binding Cassette

Heat Shock Proteins

Presenilin

$\alpha$ B Crystallin

.....  
Sarcomere Proteins  
(MYH7, MYBPC3, TNNT2, TPM1)

Lysosome-associated  
Membrane Protein-2

$\gamma$ -2 subunit AMP-dependent  
Protein Kinase

Desmin

Trans-Thyretin

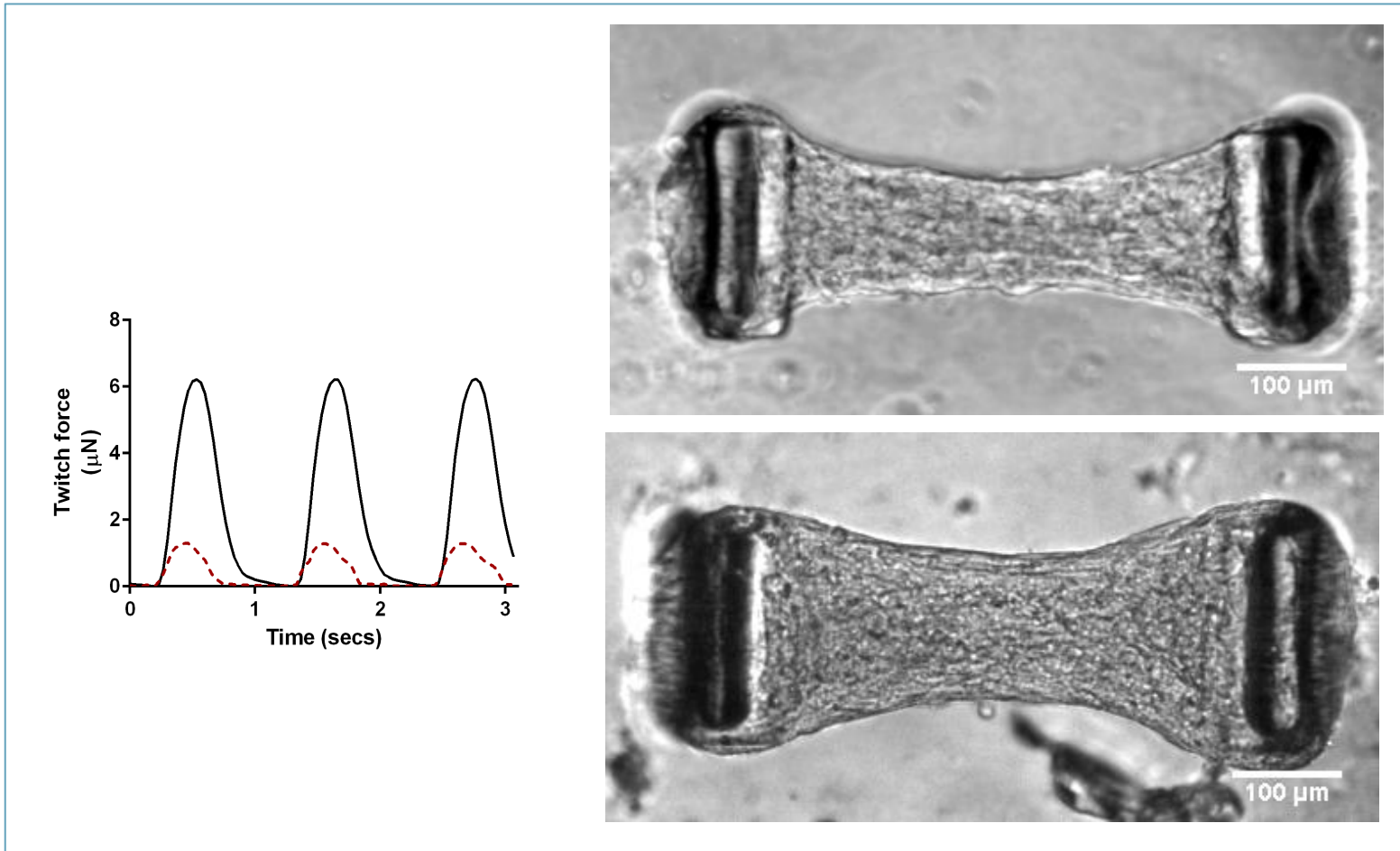
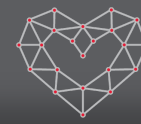
Alpha acid glucosidase

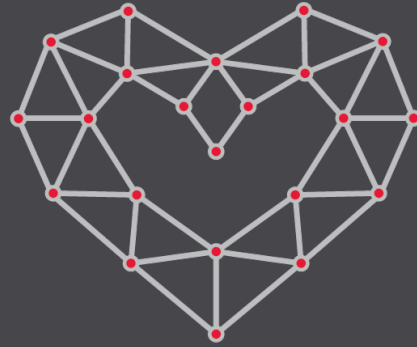
Alpha-D galactosidase

Myozenin-2

Actinin







CELL-MET

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Questions